REMARKS

The examiner has withdrawn her previous objection to the specification in light of the amendments to the specification Applicants made in response to the preceding Office Action, but she asserted that Applicants had failed to address her concern regarding the use of the trademark "Higcareen;" she questioned whether that trademark was misspelled, as she could find no information regarding that source. Applicants respectfully submit that this concern has been rendered moot by the correction set forth above to the term.

Applicants note with appreciation that the previous objections to the claims, and the rejections of the claims under § 112 have been withdrawn.

The examiner has repeated her previous rejection of claims 1-4, 7-8 and 11 under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 4,895,724, issued to Cardinal et al. (hereinafter referred to as the Cardinal reference) in view of U.S. Patent 6,214,331, issued to Vanderhoff et al. (hereinafter referred to as the Vanderhoff reference). The examiner again asserted that Cardinal discloses a porous matrix of chitosan and a macromolecular compound, which can be a polysaccharide, such as dextran or heparin, dispersed therein. The compositions are for the controlled and prolonged release of the macromolecular compounds dispersed within the chitosan matrix, and higher amounts of cross-linking are said to lower the release rate of the macromolecular compound. The examiner noted that Cardinal does not disclose the β-(1,3) glucan feature of the compositions of the present claims, but he asserted that this deficiency is provided by Vanderhoff. The secondary reference was said to

disclose a process for the preparation of aqueous dispersions of particle of water-soluble polymers, wherein cross-linking agents are used to cross-link the functional groups of the polymers. Useful polymers include polysaccharides such as curdlan, which is a β-(1,3) glucan. The examiner asserted that it would have been obvious to combine the teachings of the two references to use curdlan in the invention of Cardinal to arrive at the present invention.

In maintaining this rejection, the examiner has made two separate arguments for why the combination of these two references renders the present claims obvious. Each of these arguments is addressed below:

I. The examiner asserts that it would have been obvious to combine the teachings of the two references to use curdlan in the invention of Cardinal and that to do so would result in the present invention, because Cardinal teaches that polysaccharides such as dextran and heparin can be used as the macromolecule and Vanderhoff teaches that dextran, heparin and curdlan are all examples of polysaccharides and as such are interchangeable functional equivalents. She thus is asserting that the combination of the teachings of Cardinal and Vanderhoff would necessarily result in a composition which is the same as that presently claimed because the components making up the composition are the same as instantly claimed.

The claims of the present application are directed to compositions comprising chitosans cross-linked to glucans through diisocyanates or dialdehydes. In contrast, Cardinal's compositions comprise cross-linked chitosans with a macromolecular compound dispersed therein. Cardinal's

compositions do not comprise chitosans which are cross-linked to the macromolecules; rather, the chitosans are cross-linked to one another. Cardinal's preparations are for the controlled and prolonged release of macromolecular compounds dispersed within the chitosan matrix; the rate of release is determined not by the extent of cross-linking between the chitosans and the macromolecules, but by the extent of cross-linking between the chitosans, as noted in col. 4, line 65 - col. 5, line 2 of the Cardinal patent. It is not possible for the macromolecules to be cross-linked to the chitosan matrix--if they were so-cross-linked, the macromolecules could not be released.

The examiner is of the opinion that the macromolecules of Cardinal can be cross-linked to the chitosan matrix, based on Cardinal's statement that the matrix can be loaded with the macromolecule prior to cross-linking. The examiner seems to assume that if the matrix was loaded before cross-linking, the steps in the preparation of the Cardinal products would be the same as those claimed in the present application, such that the macromolecule would be cross-linked to the chitosan structure.

Applicants do not dispute that Cardinal teaches that the chitosan can be cross-linked either before or after loading of the matrix with the macromolecule. Applicants do disagree, however, with the examiner's assumption that if cross-linking occurs after the molecule is loaded, the macromolecule would be cross-linked to the chitosan matrix. This assumption simply is not correct. Cardinal teaches clearly that even when the cross-linking occurs after the macromolecules are added to the matrix, the macromolecules are not cross-linked to the matrix.

The examiner's attention is directed to col. 4, line 61 - col. 5, line 2, of the Cardinal patent, which explains what

happens when cross-linking is performed before the macromolecule is loaded:

> Cross-linking agents of use before loading are small sized ones such as glutaraldehyde, glyoxal, epichlorohydrin, succinaldehyde, 1, 10-decanedial, trichlorotriazine, benzoquinone, and bisepoxiranes. They are capable of penetrating the pores of the matrix and affecting the release rate. Thus, the macromolecule release rate is proportional to the extent of the cross-linking in that the more cross-linking takes place the lower the rate of release of the macromolecule.

Thus, in this embodiment, the cross-linking agents are sufficiently small that they can penetrate the pores of the matrix.

Applicants also direct the examiner's attention to col. 5, lines 8-22, of the Cardinal patent which describe the situation when cross-linking is performed after the macromolecules have been loaded into the matrix (a "loaded chitosan matrix"):

> Cross-linking agents of use in surface cross-linking a loaded chitosan matrix are macromolecular compounds having more than one aldehyde group. Such polyaldehydes are generally not capable of penetrating the chitosan matrix and affecting the macromolecule in the matrix. Any high molecular weight polysaccharide polyaldehyde may be used. Examples of useful polysaccharides are dextran, gum arabic, gum karya, pectin, carrageenan, alginic acid, and starch. Specific examples of high molecular weight cross-linking agents are oxidized polysaccharides such as dextran dialdehyde and starch dialdehyde, and dialdehydes of carrageenan or alginic acid. Synthetic polyaldehydes such as polyacrylic acid reduced to the aldehyde may be used as well.

In this scenario, the cross-linking agents are large, rather than the small agents used when the chitosan is cross-linked prior to being loaded with the macromolecule, and are "*generally not capable of penetrating the chitosan matrix and affecting the macromolecule in the matrix*" (emphasis added). Thus, Cardinal provides an explicit teaching that when cross-linking after the incorporation of the macromolecule, the choice of cross-linking agents is such that the macromolecule is not affected, i.e., cross-linked.

Attached hereto is a diagram which illustrates Cardinal's teachings when the macromolecule is loaded prior to the cross-linking. It is clear from Cardinal's discussion and the illustration attached hereto that even when the macromolecules are added to the matrix before cross-linking occurs, they are not cross-linked to the matrix. This, of course, is entirely consistent with Cardinal's provision of preparations which provide release of their macromolecular cargo.

The examiner stated in the outstanding Office Action that "[j]ust because a chemical entity is cross-linked to another chemical entity does not mean that the linkage can not be cleaved and the macromolecule can be released as there are proteases and other such molecules which are known to cleave linkages which could result in the release of the macromolecule." The examiner seems to be trying to argue that the Cardinal preparations could contain macromolecules cross-linked to the chitosan matrix and still release the macromolecules through enzymatic cleavage. This statement is entirely theoretical. As Applicants have explained above, Cardinal discloses that the macromolecular cargo should not be cross-linked to the chitosan matrix. It is not surprising, therefore, that Cardinal is silent on the subject of

enzymes which could cleave cross-linkages between the cargo and the matrix. As there are no examples or discussion of any sort of such enzymes, Applicants respectfully submit that the examiner should rely on what Cardinal actually discloses, rather than presenting her own ideas of other theoretical ways in which a slow release formulation might work. Applicants further submit that the examiner's enzymatic cleavage idea appears far-fetched at best; although the examiner suggests that proteases are one type of enzyme that could work, but it is difficult to see how a protease would help cleave a cross-linked chitosan. For such a theoretical preparation to work, it would have to encounter an appropriate active enzyme to trigger release of the macromolecule, so the effectiveness of the slow release preparations would be limited by their ability to release only the compounds when in the presence of a suitable hydrolytic enzyme. This scenario goes against the whole aim of Cardinal's invention and is not disclosed in Cardinal in any way or form.

II. The examiner's second argument focuses on preparations which would result if curdlan dialdehyde was used as a cross-linking agent in the preparations of Cardinal. Cardinal teaches that dextran dialdehyde can be used as a cross-linking agent (column 5, lines 16-21). The examiner has argued that curdlan dialdehyde could be used instead of dextran dialdehyde, since Vanderhoff discloses that dextran and curdlan are functional equivalents.

In such preparations, the curdlan and chitosan matrix are cross-linked, <u>but</u>, although cross-linked, the curdlan and chitosan in this preparation are <u>not</u> cross-linked with dialdehydes (or diisocyanates), as is required by the present

claims. Rather, each curdlan is cross-linked directly with the chitosan matrix by two separate and single aldehyde groups. This is a different arrangement from the preparations of the present claims, in which dialdehydes link the glucan to the chitosan matrix. The cross-linking of chitosans to one another by dialdehydes (curdlan dialdehydes) may be taught in the cited prior art, but the cross-linking of glucan molecules to chitosans by dialdehydes is not.

From the foregoing discussion, it is apparent that the composition of claim 1 is patentable over the Cardinal and Vanderhoff references. Similarly, claim 2 and the claims dependent from it, directed to the method of making such a composition, is distinguishable and patentable over those references for the same reasons that the composition claim is patentable. Claim 2 also is explicit that three components are mixed, whereas in the art discussed above, the curdlan dialdehyde does the job of providing the glucan and cross-linker in one component. Product by process claim 11 is patentable for the same reasons.

The examiner has maintained her previous rejection of claims 5-6 under 35 U.S.C. § 103(a) as unpatentable over the Cardinal and Vanderhoff references cited above in further view of U.S. Patent 4,879,340, issued to Moriguchi et al. She also has maintained her previous rejection of claim 9 under this same section of the statute as unpatentable over the Cardinal and Vanderhoff references in further view of U.S. Patent 6,162,537, issued to Martin et al. She further has maintained her rejection of claim 10 under 35 U.S.C. § 103(a) as unpatentable over the Cardinal and Vanderhoff references in further view of U.S. Patent

6,096,344, issued to Liu et al. Each of these rejections is traversed.

The shortcomings of the Cardinal and Vanderhoff references have been discussed above, and that discussion is equally applicable to the rejections of claims 5, 6, 9 and 10. The cited tertiary references do not compensate for the deficiencies of the primary and secondary references and are insufficient to render obvious the subject matter of these claims.

In view of the foregoing amendments and discussion, Applicants respectfully submit that the pending claims are in condition for allowance.

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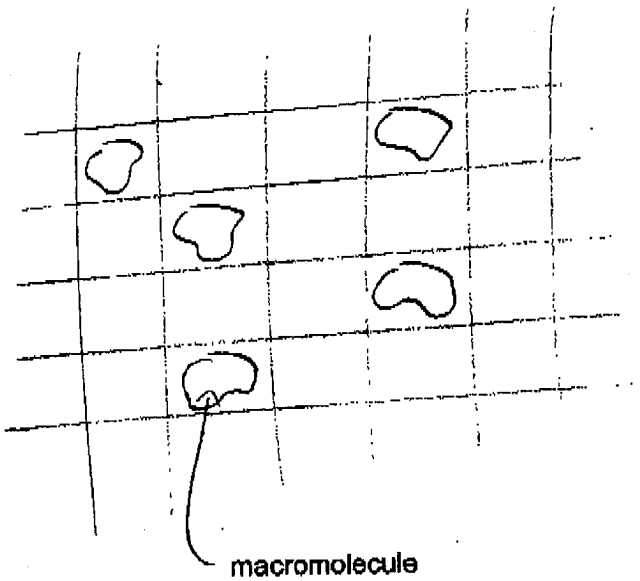
Cardinal Vanderhoff

Macromolecule added before cross linking



Add cross-linking agent to loaded chitosan matrix. Agent must be not capable of penetrating the chitosan matrix & affecting the macromolecule in the matrix e.g. those having more than one aldehyde group

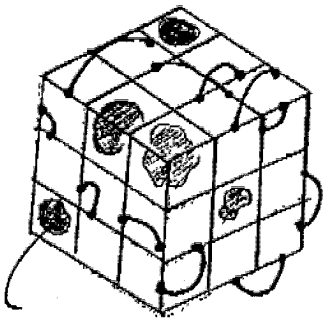
• = aldehyde group

crosslinks are on surface of matrix only.

They do not contact the macromolecule.

Macromolecule is released from matrix.

Slow release achieved by degree of chitosan-chitosan surface cross linking



macromolecule loaded into matrix

The macromolecules and the chitosans are not crosslinked to each other